Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: Is it effective?

& Research Portfolio (Volume 1)

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VOLUME I (this bound copy)

SMALL SCALE SERVICE RELATED PROJECT

Referrals to the child and family centres in Renfrewshire : A comparison of childhood psychopathology and psychosocial circumstances of affluent and deprived areas.

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Referrals to the child and family centres in Renfrewshire : A comparison of childhood psychopathology and psychosocial circumstances of affluent and deprived areas

ABSTRACT

Objective: This paper compares childhood psychopathology and psychosocial circumstances between two catchment areas of a Renfrewshire child service, selected for low and high levels of deprivation. Notions about variation of referral rates, level of multi-agency care of children, diagnoses and severity of disturbance, based on level of deprivation, were investigated.

Design: Calculation of National Deprivation Scores allowed comparison of two socially distinct areas within Renfrewshire. A broad range of child and family psychosocial variables were utilised in this comparison.

Setting: Extraction of data from a NHS Child and Family Centre database.

Subjects: Data was gathered on 314 child cases referred to the child and family centre.

Results: Findings include similar referral rates between areas and greater multi-agency service provision for deprived areas. There was greater prevalence of child abuse and conduct disorder referrals from the deprived areas. In addition, there were significant differences in severity of disturbance, with greater disturbance found in deprived areas.

Conclusions: These results are discussed with reference to social etiological factors in childhood psychopathology, such as family risk factors, the implications for preventive interventions and need for more detailed consideration of children who adapt and cope in environments not conducive to mental health.

INTRODUCTION

A long historical association links adverse circumstances and experiences to psychopathology. For several centuries life experiences resulting in stress have been considered to be direct etiological agents of disorder.[1] There is epidemiological information that suggests that the prevalence of mental health problems in childhood and adolescence is increasing.[2] There has been increasing attention paid to the observation that rates of psychiatric disorder and educational problems in children and adolescents can differ greatly according to area and to living circumstances.[3]

From the wealth of research it is clear that causation of disorder in young people is extremely complex and multifactorial. It is well documented that children are psychologically at risk where there is social and cultural deprivation. It is less apparent in what way known etiological factors combine to result in symptoms.[4] Follow-up studies indicate that the effect of socio-economic disadvantage and parental dysfunction are long-lasting.[5]

It is useful to know how rates of psychiatric disorder actually differ between areas. Many ecological studies in earlier years focused on delinquency. In recent years there has been increasing interest in area differences regarding emotional, behavioural and psychological disorders in children and adolescents. Knowledge such as this is vital if we are to deepen our understanding of contributing factors to these problems and guide preventative work.

There are several reasons why there may be a difference in referral rates and in the nature of psychiatric disorders from different areas. Families from more affluent areas are unlikely to be in contact with agencies such as social work, therefore, they may need to search quite hard for the right sort of help. Fear that their child's problem may be a sign of failure on their part, may result in the problem reaching a more severe level before they seek help.

It could be suggested that child psychiatric referral rates are higher in lower social status areas. It must be asked if this difference lies in the prevalence of disorder or the likelihood of detection. There is an assumption that there will be more multiagency involvement in such an area. There are therefore potentially more people who can make a referral and the

threshold for referral may be lower. Steinhausen and Erdin[6] found that among diagnoses, the strongest correlations with psychosocial conditions existed for conduct disorders and mixed disorders of conduct and emotions. In addition, if the disorder is linked to a higher level of social deprivation that does not change, it is possible that children from this area will show a poorer outcome.

OBJECTIVES

To compare referrals to the two Child and Family Centres within Renfrewshire NHS Trust from an affluent area of Renfrew with a more deprived area. The following hypotheses are addressed by the study:

- The deprived area will have a higher incidence of referrals than the more affluent area;
- There will be less multi-agency involvement in the more affluent area and consequently these referrals will include individuals with a more severe problem at initial assessment;
- There will be a difference in types of referrals from the two different areas of Renfrew. Conduct disorders and mixed disorders of conduct and emotion will be more common in the more deprived area;
- There will be a difference in the type of associated abnormal psychosocial circumstances of the two areas. The more deprived area will be more psychosocially disabled on a global assessment;
- Children from the more deprived area will have a more severe disturbance on discharge and will be perceived by clinicians to have a poorer global outcome.

DESIGN

Deprivation Scores have been calculated for postcode areas in the UK, which range from one (affluent) to seven (deprived). Referrals that had a deprivation score of one or two were selected to constitute the affluent Area A. Referrals that had a deprivation score of five or six were selected to form the more deprived Area B. (Referrals with a deprivation score of seven were excluded due to the very small number). Referrals from these areas to the Child and Family Centres between March 1st 1995 and March 1st 1996 were examined.

For each child, a Child and Adolescent Psychiatric Services National Audit Scorecard has been completed. Responses are based on referral information and interviews by the psychiatrist or other profession mainly involved. This information is stored in the department on dbase IV.

The following items were selected from the National Audit Scorecard for analysis:

- Sex;
- Stage of schooling;
- Previous referral;
- Other agency actively involved;
- Child's carers;
- Carer's occupation;
- Parental drug/alcohol abuse;
- Physical abuse;
- Sexual abuse;
- Emotional abuse;
- ICD-10 Axis I Clinical Psychiatric Syndromes - principle diagnosis;
- ICD-10 Axis V Associated Abnormal Psychosocial Situation;
- ICD-10 Axis VI Global Assessment of Psychosocial Disability;
- Severity of individual's disturbance at initial assessment as diagnosed on Axis I;
- Severity of individual's disturbance at discharge as diagnosed on Axis I;
- Global outcome of child (clinician's rating).

Information with regards to the population of children and young people in Argyll and Clyde was provided by Information Services within Renfrewshire NHS Trust.

RESULTS

(i)The Children

Information from the 1991 Census was updated in 1993 with regards to the population of children and young people. This information indicated that in 1993 there were 110,699 individuals aged from 0-19 years within Argyll and Clyde. It should be noted that this figure includes young people aged 19 years who would not be eligible for referral to the Child and Family Services. In 1993 the more affluent Area A, which is comprised of deprivation scores one and two, included 19,750 children and young people aged 0-19 years. The more deprived Area B, which is comprised of deprivation scores five and six, included 36,049 children and young people of that age.

During the specified one-year period a total of 314 National Audit Scorecards were completed for children seen by clinicians. Of the 109 referred from Area A, 56 (51%) were male and 53 (49%) were female. Of the 205 referred from Area B, 120 (58%) were male and 85 (42%) were female.

The above information on population size was used to estimate the referral rate from the two areas. Both Area A and Area B had a referral rate of 0.6% from the child population.

The majority of children referred from both areas were of primary school age (Area A=43%, Area B=46%) and secondary school age (Area A=45%, Area B=38%). Eight percent of children from Area A were of pre-school age, as were 15% from Area B.

Twenty seven percent of children from Area A and 28% from Area B had previously been referred to this service. Five percent from Area A and 4% from Area B had previously been referred to another psychiatric or psychological service.

Other agencies were actively involved with 30% and 46% of children from Area A and

Area B respectively.

(ii) The Parents/Carers

Insert Table 1. here.

As described in Table 1. (see Appendix 1.2), most children from Area A were cared for by both parents. In Area B most children were cared for by either a single parent, one parent plus another adult or some other adult(s).

Insert Table 2. here.

Table 2.(see Appendix 1.2) shows that more male and female carers were unemployed in Area B than Area A, as indicated by the National Audit Scorecard.

In Area A, 6% of parents/carers abused drugs and/or alcohol compared to 11% of parents/carers from Area B, as indicated by the National Audit Scorecard.

(iii) The Difficulties Children Experienced

Four percent of children from Area A were known to have been physically abused, compared with 6% from Area B. This result did not reach statistical significance (χ =3.53, df=1, p>.05). Six percent were known to have been sexually abused from Area A in comparison to 11% from Area B. Again, this result did not reach statistical significance (χ =1.34, df=1, p>.05). None of the children from Area A were known to have been emotionally abused. However, 8% of children from Area B were known to have been emotionally abused. This association between area and emotional abuse was found to be significant (χ =5, df=1, p<.05). Children could be abused in more than one way.

Insert Table 3. here.

If a clinical classification was appropriate, this was made using ICD-10 Axis I for Clinical Psychiatric Syndromes.[7] The most frequent principal diagnoses are detailed in Table 3. (see Appendix 1.2)

More children from Area A than Area B had no clinical psychiatric syndromes. Conduct disorders and mixed disorders of conduct and emotion, were the most frequently diagnosed for Area A and Area B; Area B had a higher percentage of diagnoses concentrated in these disorders. Emotional disorders were more equally diagnosed between the two groups. Mood and adjustment disorders were more common for Area A.

Insert Table 4. here.

Table 4. (see Appendix 1.2) describes the severity of the individual's disturbance at both initial assessment and discharge, as diagnosed on Axis I. At initial assessment, 46% of children from Area A were deemed 'psychologically normal' or experiencing 'trivial or minor abnormalities only', compared to 32% from Area B. Area B referrals revealed that 68% of children were experiencing 'slight', 'moderate' or 'marked' disorders in comparison to 54% from Area A. This association between area and the severity of disturbance at initial assessment was found to be significant (χ =6.29, df=1, $p<.05$).

(iv) Associated Abnormal Psychosocial Situation

Insert Table 5. here.

The most frequent principle abnormal psychosocial situation for both Area A and Area B was 'Abnormal family relationships', followed by 'Abnormal qualities of upbringing' and 'Mental disorder within the family'. 'Abnormal immediate environment' and 'acute life events' were the next most frequent categories for both areas (see Appendix 1.2).

Insert Table 6. here.

Table 6. (see Appendix 1.2) describes ICD-10 Axis VI Global Assessment of Psychosocial Disability. Sixty percent of referrals from Area A fell within the 'normal' to 'moderate functioning' range, compared to 41% of referrals from Area B. Forty percent of referrals from Area A fell within the 'slight to serious disability' categories compared to 56% of Area B. This association between area and degree of psychosocial disability was found to be highly significant (χ =8.56, df=1, $p<.01$).

(v) Outcome

At discharge, as detailed in Table 4., 58% of children from Area A were considered 'psychologically normal' or experiencing 'trivial' or 'minor abnormalities only' compared to 14% from Area B. Twenty percent of children from Area A continued to experience 'slight', 'moderate', or 'marked' disorder compared to 56% of Area B.

Clinicians gave children a 'Global outcome rating' where applicable as described in Table 7. (see Appendix 1.2). Eighteen percent of children from both areas showed 'no change'. Nine percent from both areas were 'slightly improved'. Twenty-five percent from Area A and 29% from Area B were considered to have 'improved'. Seventeen percent from Area A and 11% from Area B were deemed 'much improved'. Six percent from Area A had 'recovered', compared with 1% from Area B. Again, it is noted that a substantial proportion of the information was 'missing or unknown'.

CONCLUSIONS

The first hypothesis that the more deprived Area B would have a higher incidence of referrals than the more affluent Area A, was not supported when the size of the population of children and young people was taken into account. Both areas had the same incidence of referrals. One possible explanation for this is that the agencies involved are likely to be in contact with the families in greatest need or with children experiencing the greatest difficulties. It is possible that there are families and children whose difficulties are of a less severe nature and who consequently do not come to the attention of a potential referring agent. In addition, this study does not take into account the resources and services that are available locally for families.

The second hypothesis that there would be less multi-agency involvement in the more affluent Area A was supported. This hypothesis also stated that individuals from Area A would present with a more severe problem as a result of less multi-agency involvement. This was not found to be the case. Children from Area B were experiencing significantly more 'slight', 'moderate' and 'marked' disorders at initial assessment. Therefore, although there is more multi-agency involvement in Area B and presumably an increased likelihood

of detection, children from Area B present with a more severe disturbance at initial assessment. Possible reasons for this become apparent when risk factors, which these children are subjected to, are discussed.

The third hypothesis asserted that there would be a difference in types of referral from the two areas. Specifically, conduct disorders and mixed disorders of conduct and emotion are more common in the more deprived area. However, it was found that conduct disorders and mixed disorders of conduct and emotion were the most frequent principle diagnosis for both areas. The difference was that a greater percentage of children from Area B were represented by these disorders. Berelowitz and Nelki[8] note that conduct disorders are much more common in boys and that children tend to come from a disadvantaged background; which could explain this finding. More children from Area A did not have a diagnosed psychiatric syndrome.

The fourth hypothesis stated that there would be a difference in the type of associated abnormal psychosocial circumstances of the two areas and that the more deprived area would be more psychosocially disabled on a global assessment. The results indicate that both areas share the same type of psychosocial characteristics. However, the ICD-10 Global Assessment of Psychosocial Disability[7] distinguishes between the two areas in that a significantly greater proportion from Area B fall within the 'disability' categories.

The fifth hypothesis maintained that children from Area B would have a more severe disturbance on discharge. In addition, it was postulated that children from Area B would be perceived by the clinicians to have a poorer Global Outcome. Although Farrington[3] states that the impact of socio-economic disadvantage and parental dysfunction has long-lasting negative effects, conclusions cannot be drawn due to the substantial proportion of data missing or unknown.

Additional information allows consideration of possible reasons for differences between Area A and Area B. Pearce[9] recognises that there are 'child risk factors' which include genetic influences, specific developmental delay, difficult temperament and physical illness among others. He also identifies 'family risk factors' which include family breakdown, physical, sexual, and emotional abuse, parental drug and alcohol abuse; all of which have been demonstrated to be more frequent in Area B, putting these children at

increased risk.

Pearce also details 'environmental risk factors' which includes socio-economic disadvantage which children from Area B experience to a greater extent. This situation is likely when carers are unemployed, divorced or living alone. Again, all of these situations are more frequently found in referrals from Area B.

Stone and Koupernik[10] maintain that "where social and cultural deprivation exist, children are psychologically at risk" as has been demonstrated in this study. Williams and Richardson[2] state that no one profession or agency alone can hope to comprehend all the issues or be responsible for every response. It is essential that children's mental health and social problems are met with close collaboration between a wide variety of agencies.

It is vital to recognise that there are characteristics of certain environments which will put children at risk and of certain adults which predict that they will have difficulty parenting.[2] This would suggest that children vulnerable to mental health problems could be identified prior to birth, which highlights the need for preventative work.

Several authors[11] have noted that many children who suffer adverse circumstances and risk factors do not actually develop problems or disorders. Factors such as self- esteem, sociability, absence of parental discord and social support systems protect children. As professionals we have much to learn from children who cope, and even flourish, in adverse circumstances. This is an area for further essential research.

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MAJOR RESEARCH PROJECT LITERATURE REVIEW

Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: A review

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(see Appendix 2.1 for instructions to authors)

Should symptomatically hypothyroid but biochemically euthyroid patients be treated with thyroxine? : A review

Abstract

There is a wealth of literature regarding the treatment, psychiatric and neuropsychological concomitants of clinical and subclinical hypothyroidism. However, polarised arguments about the utility of treating patients who are symptomatically hypothyroid, but biochemically euthyroid have recently occurred, in the absence of any clinical trials. This review highlights current scientific understanding concerning the treatment of hypothyroid disorders. In addition, the need for a scientific clinical treatment trial to establish whether symptomatically hypothyroid, but biochemically euthyroid patients should be treated with thyroxine is emphasised.

Key Words: Symptomatically Hypothyroid, Biochemically Euthyroid, Double-blind, Placebo Controlled, Treatment Outcome Trial, Thyroxine, Cognitive Function, Psychological Health

Introduction

The thyroid is the ductless gland found on both sides of the trachea. It secretes predominantly thyroxine (T4), and a small amount of triiodothyronine (T3). Production of T3 and T4 in the thyroid is stimulated by thyrotrophin (thyroid-stimulating hormone, TSH). Ingbar and Woeber[1] state that the thyroid hormones play upon a great multiplicity of metabolic processes: influencing the concentration and activity of numerous enzymes;

the metabolism of substrates, vitamins and minerals; the secretion and degradation rates of virtually all other hormones; and the response of their target tissues to them. As a consequence, it can truly be said that no tissue or organ system escapes the adverse effects of thyroid hormone excess or insufficiency. Hypothyroidism is the result of structural or functional abnormalities of the thyroid gland leading to thyroid hormone deficiency. It is therefore characterised by a raised TSH and a low level of T4. Subclinical hypothyroidism is defined as an elevated resting level of TSH in the context of normal T4. Euthyroid is the term applied when thyroid function tests, including TSH are within the reference range.

Recently, there has been increasing interest in a group of patients who present as symptomatically hypothyroid but biochemically euthyroid. This review will consider whether these patients should be considered for thyroxine replacement treatment. Firstly, the literature regarding the clinical features, psychiatric and neuropsychological manifestations of clinical hypothyroidism will be discussed. Secondly, the same areas will be reviewed in relation to subclinical hypothyroidism. Thirdly, the treatment of clinical hypothyroidism and subclinical hypothyroidism will be considered. Finally, the current debate concerning thyroxine replacement in symptomatically hypothyroid, but biochemically euthyroid patients will be outlined.

Clinical Hypothyroidism

Clinical features associated with hypothyroidism include tiredness, lethargy, weight gain, coarsening of the skin, intolerance to cold, hair loss, dry hair, hypersomnolence and delayed reflexes.[2] Several authors argue that the non-specific nature of the signs and

symptoms of hypothyroidism means that biochemical tests of thyroid function (specifically TSH) are an essential component of the diagnosis.[3,4]

Psychiatric symptoms are reported to be a common clinical complication of thyroid disorders.[5,6] Hypothyroidism has long been known to induce mania, dementia and dementia like features. In particular, it has frequently been described as accompanied by depressive symptoms.[7] Haggerty and Prange[8] report that almost 100% of patients with severe hypothyroidism are found to have serious concurrent depression. Whybrow and Ferral[5] reported that in a group of seven hypothyroid patients the predominant affective disturbance was a marked depression of mood. Jain[9] assessed 30 consecutive patients diagnosed as hypothyroid and judged 13 patients to be clinically depressed.

In addition, patients who are hypothyroid have been reported to suffer from impairment of cognitive functions, such as recent memory, attention, inability to concentrate and mental slowing.[10,11] Osterweil, Syndulko, Cohen et al.[12] concluded that hypothyroidism in non-demented older adults is associated with impairments in learning, word fluency, visual-spatial abilities, and some aspects of attention, visual scanning and motor speed. Leentjens and Kappers[13] add lack of initiative to the list of affected cognitive symptoms and Mennemeier, Garner, Heilman et al.[14] include problem solving abilities. Denicoff, Russel, Lakshmanan et al.[10] state that the capacity to perform simple calculations is impaired.

Subclinical Hypothyroidism

Jaeschke, Guyatt, Gerstein et al.[15] found that patients with subclinical hypothyroidism

experienced similar symptoms to those with hypothyroidism: physical complaints; reduction in energy and well being; disturbance of mood and emotions; and deficits in cognitive functions.

To elaborate, evidence indicates that subclinical hypothyroidism may be a risk factor for depression.[8] This idea was initially put forward by studies which examined rates of thyroid laboratory abnormalities in psychiatric patients. Subclinical hypothyroidism has been found in 5-15% of depressed patients.[16,17,18] Antithyroid antibodies have been found in 9-20% of depressed psychiatric patients.[19,20] The rates of thyroid laboratory abnormalities in all of these studies were high compared with reported population norms. However, most studies did not use control groups, which represents an important weakness because the prevalence of thyroid dysfunction is highly influenced by age and gender. The one controlled study to date, compared age and sex controlled antibody rates in psychiatric inpatients and general medical outpatients and found an elevated rate of antithyroid antibodies in subjects with bipolar depression, but not in those with unipolar depression.[21]

Only recently have studies been conducted in which psychiatric evaluations were performed in specified groups of patients with endocrine disorders. To date, such data strengthen the less well-controlled findings from psychiatric subjects. Haggerty, Marquardt, McAllister et al[22] screened thyroid function in 148 general medical patients and found a history of treatment for depression in 50% of those with higher TSH values compared with 18% of those with lower TSH values. In a second study by Haggerty, Stern, Mason et al.[23], blind psychiatric assessments with structured diagnostic interviews revealed a nearly threefold higher lifetime prevalence of depression in those with subclinical hypothyroidism (56%) than those found to be euthyroid (18%). In geriatric

populations the association appears to be even more striking. Esposito, Haggerty, Stern et al.[24] examined routinely obtained laboratory data on 163 patients over the age of 65 who were followed in a geriatric medical evaluation clinic. Of these, 9% had thyroid function test results consistent with the diagnosis of subclinical hypothyroidism. Seventy-five percent of patients had a lifetime history of major depression, compared with 18% of euthyroid patients.

Haggerty and Prange[8] conclude that, in contrast to overt hypothyroidism, subclinical hypothyroidism is probably not a sufficient cause of depression. Rather it may work in concert with other risk factors to increase the likelihood that episodes of this recurrent disorder will occur when, and if, other vulnerability factors are also present.

Monzani, Del Guerra, Caraccio et al.[7] note that only scant data is available concerning neuropsychological abnormalities in subclinical hypothyroidism. These authors assessed selected neuropsychological features by means of standardised tests in a group of patients with subclinical hypothyroidism who were free from subjective neuropsychological complaints. Significant impairment was demonstrated in patient's memory-related abilities, namely short-term memory, digit span and visual memory. However, it should be noted that this study has a small sample size (n=14) and the researchers were not blind to the treatment received by the patients. Jaeschke at al.[15] established that with regards to cognitive function, patients with subclinical hypothyroidism displayed difficulties in remembering and felt mentally slower. No control group was used in this study. Haggerty, Stern, Beckwith et al.[25] state that subjects with subclinical hypothyroidism tend to perform more poorly than euthyroid subjects on measures of verbal recall, visuospatial recall and attention. These findings are reported to parallel data from clinical populations indicating

that subclinical hypothyroidism may have important neuropsychiatric consequences.

Benefits of Thyroid Replacement in Clinical Hypothyroidism and Subclinical Hypothyroidism

Jaeschke et al.[15] state that thyroid replacement is clearly beneficial once T4 falls (overt hypothyroidism). Thyroid hormone replacement therapy appears to be associated with improvements in mood.[26,10,27] Improved functioning has been shown in selected areas of cognitive function such as attention, concentration, learning, retention and word fluency.[12] However, although a control group was employed the study did not include a placebo. Mennemeier, Garner and Heilman[14] state that the link between replacement therapy and improved cognitive functions is tentative. It has been argued by some that the cognitive symptoms due to hypothyroidism may not be reversible.[13,14] They report that only a few studies used unselected patient populations and psychological tests to assess cognition.[27,10,28,29] Two noted improvements in general intelligence following treatment.[27,28] Two others found no change in non-verbal intelligence, attention, or general cognitive function.[10,29] No study used a combination of treatment design and control subjects which was adequate to rule out practice effects, nor did any study use detailed neuropsychological tests of intelligence or memory.

Jaeschke et al.[15] state that thyroid replacement for patients with subclinical hypothyroidism remains controversial. Haggerty et al.[25] argue that while there is some evidence for long-term health consequences of subclinical hypothyroidism, we do not yet know enough about the relative risks versus benefits of long-term thyroid hormone administration in this

disorder to justify routine treatment in all cases. However, these authors add that there is good reason to consider a trial of thyroid hormone treatment for cases of subclinical hypothyroidism that are accompanied either by mood or energy changes or by treatment resistant major affective disorder.

Thyroid hormone has been shown to reverse depressive symptomatology in patients with subclinical hypothyroidism.[30] Two double-blind trials in patients with subclinical hypothyroidism have shown that, after treatment with thyroxine, target organ function may improve and there may be a greater sense of well-being in some but by no means all.[31] However, Beckett and Toft[32] report that the consensus is that patients with subclinical hypothyroidism should be treated with thyroxine.

Weetman[4] summarises the few recent neuropsychological studies of patients with subclinical hypothyroidism. One small crossover trial has indicated that thyroxine improves symptom scores (including mental lethargy) and psychometric performance compared with a placebo in 20% of women.[33] However, there are a number of difficulties with this study: there was no control group; they did not utilise a comprehensive set of psychometric tests; the study design did not include a wash-out period, which means that there is the risk of a carryover effect of the first drug into the second treatment period; and finally, the placebo was prescribed in a different manner to thyroxine. Although the above study has limitations, the improvements in functioning reported are supported by a study which included patients previously treated for hyperthyroidism[31] and by a prospective, unblinded trial of thyroxine in patients with subclinical hypothyroidism.[7] This latter study found an improvement in memory skills. Jaeshke et al.[15] found a statistically significant improvement in a composite memory score in actively treated patients with subclinical

hypothyroidism versus controls. However, the method of deriving this composite memory is unclear.

Symptomatically Hypothyroid but Biochemically Euthyroid Patients: The Current Debate

In the past two years there has been vehement debate in the field of thyroid disease. Skinner, Thomas, Taylor et al.[34] have questioned current medical practice stating that they considered it to be incorrect that "normal" free thyroxine and thyroid stimulating hormone concentrations negate the diagnosis of hypothyroidism. They also reported that it is unusual for doctors to start thyroxine replacement in clinically hypothyroid but biochemically euthyroid patients. However, it is their belief that the exclusion of hypothyroidism on the grounds of hormone concentrations measured in the laboratory seems wrong and that many patients are condemned to years of hypothyroidism with its pathological complications and poor quality of life. Skinner et al.[34] have urged that the question of biochemically euthyroid patients should be subjected to a formal clinical trial.

Shepherd[35] reported that he was aware of a number of patients with normal thyroid function being given a daily dose of thyroxine mainly as a result of publicity being given in the lay media[36] to the hypothesis put forward by Skinner.[34] Shepherd[35] is concerned that not only are patients continuing to be prescribed thyroxine, but in some cases the dose is being progressively increased. He outlines possible detrimental consequences.

Beckett and Toft[32] speculate that because autoimmune thyroid disease is common, it is

possible that reference ranges were calculated from populations containing patients with a degree of thyroid failure and that the true upper limit for normal serum thyroid stimulating hormone concentrations may be slightly lower than 5mU/l. They highlight the fact that there are no studies of the effect of thyroxine in patients with non-specific symptoms and hormone concentrations below 5mU/l, and until there is objective evidence of benefit, it would be unwise to support the views of Skinner et al.[34] Beckett and Toft[32] believe that it is unlikely, from clinical experience, that there will be evidence of benefit and that many patients would gain a placebo effect.

Beckett and Toft[32], Beastall and Thomson[37] and Shepherd[35], have urged that in the absence of any reputable evidence to support the hypothesis that clinical hypothyroidism can exist in biochemically euthyroid patients, this speculative use of thyroxine should be restricted to a carefully supervised trial.

McLaren, Kelly and Pollock[38] report that several symptomatically hypothyroid but biochemically euthyroid patients referred to a clinic following the recent publicity, complained of considerable reduction in their quality of life which had not been helped by other measures. Two patients reported a marked improvement in their condition following thyroxine treatment. These authors acknowledge that this result could have been due to a placebo response and that our present state of knowledge suggests that there is no scientific justification for this treatment. However, they argued that it cannot be assumed that everything is known about the physiology of thyroid secretion and its controlling hormones, or the pharmacological effects of exogenous thyroxine.[32] In view of the lack of effective treatment for this group, further investigation of the effect of thyroxine is justified.[38]

Conclusions

To date, there is evidence that hypothyroidism and subclinical hypothyroidism result in physical complaints, reduction in energy and well-being, disturbance of mood and emotions and deficits in cognitive functions. Although research on the effects of active treatment on some of these areas is limited, there is evidence to suggest that thyroxine replacement can lead to improvements. It is evident that further research is required to provide evidence that either thyroxine is truly effective in patients who may be clinically hypothyroid but are biochemically euthyroid, or, that any improvement seen is due to a placebo effect.

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MAJOR RESEARCH PROJECT PROPOSAL

Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: Is it effective?

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Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: Is it effective?

SUMMARY

The clinical features of hypothyroidism are non-specific and biochemical tests of thyroid function are considered essential for diagnosis. Recent articles in the local press have suggested that there are a large number of patients who are clinically hypothyroid but biochemically euthyroid and who would benefit from thyroxine replacement (Reid, 1997). This has led to correspondence in the British Medical Journal (Beastall and Thompson, 1997; Beckett and Toft, 1997; McLaren, Kelly and Pollock, 1997; Shepherd, 1997; Skinner, Thomas, Taylor et al., 1997). In the absence of any reputable evidence, it is unlikely that there are patients who are clinically hypothyroid but biochemically euthyroid. However, a properly controlled trial is required. This is a randomised, double blind, crossover, placebo-controlled trial to investigate the efficacy of thyroxine replacement in a group of such patients. Twenty-two patients and nineteen control subjects will take part in the study at Stobhill General Hospital. Standardised psychological self-rating questionnaires and objective neuropsychological tests will determine the efficacy of thyroxine treatment.

INTRODUCTION

The thyroid is the ductless gland found on both sides of the trachea. It secretes thyroxine (T4) that controls the rate of metabolism. Hypothyroidism is the result of structural or functional abnormalities of the thyroid gland leading to thyroid hormone deficiency. It is therefore, characterised by a raised thyroid stimulating hormone (TSH) and a low level of thyroxine. Subclinical hypothyroidism is defined as an elevated resting level of thyroid stimulating hormone in the context of normal thyroxine.

Clinical features associated with hypothyroidism include: tiredness; lethargy; weight gain; coarsening of the skin; intolerance to cold; hair loss; dry hair; hypersomnolence; and delayed reflexes. Several authors have argued that the non-specific nature of the signs and symptoms of hypothyroidism means that biochemical tests of thyroid function (specifically TSH) are an essential component of the diagnosis (e.g., Vanderpump, Ahlquist, Franklyn et al., 1996; Weetman, 1997). Psychiatric symptoms are reported to be a common clinical complication of thyroid disorders (Whybrow and Ferral, 1974). In particular, hypothyroidism has frequently been described as accompanied by depressive symptoms (Monzani, Del Guerra, Caraccio et al., 1993). In addition, patients who are hypothyroid have been reported to suffer from impairment of cognitive functions, such as recent memory, attention, inability to concentrate and mental slowing (Denicoff , Russell, Joffe et al., 1990; McGregor, 1996).

Jaeschke, Guyatt, Gerstein et al. (1996) found that patients with subclinical hypothyroidism experienced similar symptoms to those with hypothyroidism: physical complaints; reduction in energy and wellbeing; disturbance of mood and emotions; and deficits in cognitive

function.

Jaeschke et al. (1996) stated that thyroid replacement is clearly beneficial once T4 falls (overt hypothyroidism) but that thyroid replacement for patients with subclinical hypothyroidism remains controversial. However, Beckett and Toft (1997) reported that the consensus is that patients with subclinical hypothyroidism should be treated with thyroxine. One double-blind trial in patients with subclinical hypothyroidism have shown that, after treatment with thyroxine, target organ function may improve and there may be a greater sense of wellbeing in some, but by no means all patients (Cooper, Halpern, Wood et al., 1984). Thyroid hormone has been shown to reverse depressive symptoms in patients with subclinical hypothyroidism (Goodnick, Extein and Gold, 1989).

In recent years, few studies have assessed the benefit of thyroid replacement therapy on cognitive function in hypothyroidism, but improved functioning has been shown in selected areas such as attention, concentration, learning, retention and word fluency (Osterweil, Syndulko, Cohen et al., 1992).

Weetman (1997) summarised the few recent neuropsychological studies of patients with subclinical hypothyroidism. One small crossover trial has indicated that thyroxine improves symptom scores (including mental lethargy) and psychometric performance compared with a placebo in 20% of women (Nystrome, Caidahl, Fager et al., 1988). This trial is supported by a study which included patients previously treated for hyperthyroidism (Cooper, 1984) and by a prospective, unblinded trial of thyroxine in patients with subclinical hypothyroidism (Monzani et al., 1993). This latter study found an improvement in memory skills. Jaeshke et al. (1996) found a statistically significant improvement in a composite memory score in

actively treated patients with subclinical hypothyroid versus controls.

In the past two years there has been vehement debate in the field of thyroid disease. Skinner et al (1997) stated that it is unusual for doctors to start thyroxine replacement in clinically hypothyroid but biochemically euthyroid patients. However, he reported that the exclusion of hypothyroidism on the grounds of hormone concentrations measured in the laboratory seems wrong and that many patients are condemned to years of hypothyroidism with its pathological complications and poor quality of life.

Shepherd (1997) reported that he was aware of a number of patients with normal thyroid function being given a daily dose of thyroxine mainly as a result of publicity being given in the lay media (Reid, 1997) to the hypothesis put forward by Skinner (1997). Several authors have urged that in the absence of any reputable evidence to support the hypothesis that clinical hypothyroidism can exist in biochemically euthyroid patients, the speculative use of thyroxine should be restricted to a carefully supervised trial (Beastall, 1997; Beckett and Toft, 1997; Shepherd, 1997).

McLaren, Kelly and Pollock (1997) stated that patients reporting a considerable improvement after thyroxine treatment could be due to a placebo response. However, they argued that it cannot be assumed that everything is known about the physiology of thyroid secretion and its controlling hormones, or the pharmacological effects of exogenous thyroxine (Beckett and Toft, 1997).

AIM OF THE STUDY

The aim of this study is to determine whether thyroxine treatment has an effect on the cognitive functioning, psychological and physical wellbeing of patients who are symptomatically hypothyroid but biochemically euthyroid.

PLAN OF INVESTIGATION

Subjects

The trial will involve 22 patients between the ages of 22 and 73 years. Patients will be recruited following referral by their General Practitioner, other clinicians, or by self-referral following newspaper publicity (Appendix 3.1). They will be considered for the study if, for a period of at least the previous six months, they have exhibited at least three of the following signs and symptoms for which no other cause can be elicited: tiredness; lethargy; weight gain or inability to lose weight; cold intolerance; hair loss; and dry skin or dry hair. All patients will have thyroid function tests, including TSH, within the reference range. Persons with known cardiovascular disease, hepato/renal failure, pregnancy or thyroid dysfunction will be excluded. The trial will involve 19 age and sex matched control subjects who will be normal volunteers.

Measures

Biochemical

The medical team will assess the following:

At Baseline: Thyroid stimulating hormone (TSH); thyrotrophin-releasing hormone (TRH); thyroxine (T4); triiodothyronine (T3); free thyroxine (FT4); anti-thyroid peroxidase; anti-thyroglobulin antibodies; prolactin; cholesterol; lipids; full blood count; electrolytes; liver function; weight; blood pressure; and pulse.

At Weeks 12 and 30: Free T4 (FT4); prolactin; cholesterol; weight; blood pressure; and pulse.

Psychological Assessment Measures

The following psychological assessment measures will be administered at baseline and repeated at weeks 12 and 30, to assess quality of life concepts: Hospital Anxiety and Depression Scale (HADS; Zigmund and Snaith, 1983); Social Functioning Questionnaire (SF-36; Ware, 1997); and the Fatigue Scale (Chalder, 1993). A number of cognitive tests will also be administered: the Digit Span, Logical Memory, Visual Reproduction and Verbal Paired Associates subtests from the Wechsler Memory Scale - Revised (WMS-R; Wechsler, 1987); and Trail Making Test (Reitan, 1966). A description of each assessment measure is given in Appendix 3.2.

Design and Procedure

This is a randomised, double blind, crossover, placebo-controlled trial. Subjects who agree to take part in the study will be given an information sheet and will be asked to sign a consent form (see Appendix 3.3). Participants in the study will be randomised at the first clinic visit. Each group (patients and controls) will receive placebo or 100μg thyroxine for three months followed by a six-week washout period. They will then crossover and receive a further three months of treatment (either thyroxine or placebo). The Pharmacy Department who will hold the key to the randomisation will dispense the drugs.

Setting and equipment

Patients will be assessed at Stobhill General Hospital. For the psychological component of the study, the appropriate questionnaires, materials and scoring sheets for the WMS-R subtests and Trail Making Test will be required.

Data analysis

Data will be collated first on a paper summary sheet for each individual and than transferred to a database. Statistical analyses will involve independent t-tests and paired t-tests.

PRACTICAL APPLICATIONS

In response to recent correspondence in the British Medical Journal from a number of

eminent practitioners in the field of thyroid disease and the considerable demand for treatment, this study will provide evidence as to whether thyroxine treatment is effective in symptomatically hypothyroid but biochemically euthyroid patients.

TIMESCALES

The placebo is scheduled to be available from February 1998. No difficulty is anticipated with recruitment of subjects given local interest. Data collection will be complete seven months after the inclusion of the final subject.

ETHICAL APPROVAL

The study has received ethical approval from the Stobhill General Hospital Ethics Committee.

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MAJOR RESEARCH PROJECT PAPER

Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: Is it effective?

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Target Journal: New England Journal of Medicine (See Appendix 4.1 for instructions to authors)

This research study was established by Dr Pollock, Principal Biochemist, Stobhill General Hospital. The neuropsychological component of the study was developed by the author. All psychological components of the study were conducted by the author.

Thyroxine replacement in symptomatically hypothyroid but biochemically euthyroid patients: Is it effective?

Abstract

Background The treatment of patients who present as symptomatically hypothyroid but biochemically euthyroid is the subject of current debate. Accepted medical practice has been questioned, with the assertion that it is incorrect that normal thyroid function tests negate the diagnosis of hypothyroidism.[1] Some of these patients have been treated with thyroxine in the absence of any experimental trials.[2] This is the first known trial to investigate whether thyroxine treatment has an effect on the cognitive functioning, psychological and physical wellbeing of patients who are symptomatically hypothyroid but biochemically euthyroid.

Methods This study compared 22 symptomatically hypothyroid but biochemically euthyroid patients' and 19 matched control subjects' responses to thyroxine, in a randomised, double

blind, crossover, placebo-controlled, trial. A range of standardised biochemical and psychological measures were employed at baseline, prior to random allocation to thyroxine or placebo. Assessment measures were repeated at the end of both 12-week treatment periods. There was a six-week washout period between treatments.

Results At baseline, patients were significantly more impaired than control subjects on the majority of psychological and cognitive measures. Thyroxine treatment did not have a significant beneficial effect on the cognitive functioning, psychological and physical wellbeing of patients who were symptomatically hypothyroid but biochemically euthyroid.

Conclusions Symptomatically hypothyroid but biochemically euthyroid patients do not benefit from treatment with thyroxine. It is suggested that on the basis of this evidence, there is no justification for the routine prescription of thyroxine.

Key Words: **Symptomatically Hypothyroid, Biochemically Euthyroid, Double-blind, Placebo Controlled, Treatment Outcome Trial, Thyroxine, Cognitive Function, Psychological Health.**

Introduction

In the past two years there has been vehement debate in the field of thyroid disease concerning the treatment of patients who present as symptomatically hypothyroid but are biochemically euthyroid, i.e., they have the non-specific features of hypothyroidism but their thyroid function tests are within the reference range. Skinner, Thomas, Taylor et al.[1] have questioned current medical practice, stating that the exclusion of hypothyroidism on the grounds of hormone concentrations measured in the laboratory is wrong and that many patients are condemned to years of hypothyroidism with its pathological complications and poor quality of life. Shepherd[2] reported that he was aware of a number of patients with normal thyroid function being given a daily dose of thyroxine (T4) mainly as a result of publicity in the lay media[3] to the hypothesis put forward by Skinner, Thomas, Taylor et al.[1] Shepherd[2] was concerned that not only were patients continuing to be prescribed thyroxine, but in some cases the dose was being progressively increased. He outlined possible detrimental consequences, for instance, there could be increased strain on the heart or osteoporosis might develop. McLaren, Kelly and Pollock[4] reported that two

symptomatically hypothyroid but biochemically euthyroid patients, not helped by any previous treatment, reported a marked improvement in their condition following thyroxine treatment. They acknowledged that improvements could have been due to a placebo effect and that the present state of knowledge suggested that there was no scientific justification for such treatment.

Descriptions of the thyroid gland, hypothyroidism and subclinical hypothyroidism disorders are given in Chapter 2 (Major Project Literature Review). Clinical features associated with hypothyroidism include: tiredness; lethargy; weight gain; coarsening of the skin; intolerance to cold; hair loss; dry hair; hypersomnolence; and delayed reflexes. Psychiatric symptoms are reported to be a common clinical complication of thyroid disorders.[5] In particular, hypothyroidism has frequently been described as accompanied by depressive symptoms.[6] In addition, patients who are hypothyroid have been reported to suffer from impairment of cognitive functions, such as recent memory, attention, inability to concentrate and mental slowing.[7,8] Jaeschke, Guyatt, Gertein et al.[9] found that patients with subclinical hypothyroidism experienced similar symptoms to those with hypothyroidism: physical complaints; reduction in energy and wellbeing; disturbance of mood and emotions; and

deficits in cognitive function.

Jaeschke, Guyatt, Gertein et al.[9] stated that thyroid replacement is clearly beneficial once T4 falls below the lower limit of the reference range (overt hypothyroidism), with some evidence of improvements in mood and selected areas of cognitive function. There is also evidence of similar improvements in patients with subclinical hypothyroidism following treatment with thyroxine, although some of the studies have methodological difficulties. (See Chapter 2, Major Research Project Literature Review, for a full discussion). To date, there have been no experimental studies that have assessed the effect of thyroxine on symptomatically hypothyroid but biochemically euthyroid patients.

Several authors have urged that in the absence of any reputable evidence to support the hypothesis that clinical hypothyroidism can exist in biochemically euthyroid patients, the speculative use of thyroxine should be restricted to a carefully supervised trial.[2,10,11] The aim of this randomised, double blind, placebo-controlled trial was to determine whether treatment with thyroxine had an effect on the cognitive functioning, psychological and physical wellbeing of patients who were symptomatically hypothyroid but biochemically

euthyroid.

Methods

Subjects

Patients and control subjects were invited to participate in a randomised, double blind, crossover, placebo-controlled study. The research was conducted at Stobhill General Hospital, Glasgow. The Stobhill General Hospital Ethical Committee approved the study. Each participant was provided with an information sheet and gave written consent (Appendix 3.3). Data collection commenced on March 6th 1998 and was completed on 26th March 1999.

Patients were recruited following referral by their GP, other clinicians, or by self-referral in response to an article about the study in a local newspaper (see Appendix 3.1). They were considered for the study if, for a period of at least the previous six months, they had exhibited at least three of the following common signs or symptoms of hypothyroidism, for

which no other cause could be elicited: tiredness; lethargy; weight gain or inability to lose weight; cold intolerance; hair loss; and dry skin or dry hair. All patients (with the exception of one) had thyroid function tests, free T4 (FT4) and thyroid stimulating hormone (TSH), within the reference range (9 - 25pmol/litre) and (0.1 - 5.0mU/litre) respectively. One patient had a basal TSH of 5.3mU/litre which was subsequently 4.6mU/litre following treatment with placebo. Normal full blood count, electrolyte and liver function tests were also a prerequisite of recruitment. Persons with known cardiovascular disease, hepato/renal failure, pregnancy or thyroid dysfunction were excluded.

A total of 25 patients were enrolled, and 22 patients completed the study. There were 19 age and sex-matched controls who were normal volunteers; mainly hospital personnel. An attempt was made to have an equal number of patients and control subjects, however, difficulty was experienced in the recruitment of controls. A description of the study subjects is given in Table 1. One patient withdrew from the study during the first treatment period because she was concerned about the dosage, another failed to attend her second appointment for no known reason, and a third withdrew from the study due to illness.

TABLE 1. Baseline Characteristics of the Study Subjects

	Patients (n=22)	**Controls (n=19)**
Sex:		
Male	2 (9%)	2 (10%)
Female	20 (91%)	17 (90%)
Age	48.45 ±11.2	48.94 ± 10.4
Previous Psychiatric Contact (no.)	6 (27.3%)	1 (5.3%)
Referrer:		
GP	12 (54.5%)	N/A
Self – Referral	13 (36.4%)	
Other	2 (9.1%)	
T4 Previously Prescribed	3 (13.6%)	0

Study Protocol

The Pharmacy Department randomised both patients and control subjects to receive either

thyroxine or placebo first. This randomisation to treatment order was determined by the toss of a coin at the first clinic visit. Eight patients and eleven control subjects received thyroxine first followed by placebo, while the remaining fourteen patients and eight control subjects received placebo first followed by thyroxine. The randomisation procedure ensured that all researchers were blind to treatment order allocation until the last participant had completed the treatment protocol.

The biochemical measures recorded at baseline and on return visits after 12 and 30 weeks, are given in Appendix 4.2. In order to assess psychological responses to either thyroxine or placebo, a range of psychological assessment measures, detailed below, were administered at baseline and repeated at return visits. Each participant received either placebo or thyroxine (100μg) for 12 weeks followed by a six week washout period. They then crossed-over and received a further 12 weeks of treatment. The thyroxine and placebo tablets were visually identical.

Psychological Assessment Measures

The following psychological assessment measures were administered to assess quality of life concepts: Hospital Anxiety and Depression Scale (HADS)[12] to assess emotional disorder; Social Functioning Questionnaire (SF-36)[13],a multi-item scale measuring seven health concepts; and Fatigue Scale[14] to measure the severity of fatigue. A number of cognitive tests were administered: the Digit Span, Logical Memory, Visual Reproduction and Verbal Paired Associates subtests from the Wechsler Memory Scale - Revised (WMS-R)[15], to assess attention and concentration, verbal memory and visual memory respectively. The Trail Making Test[16] was administered to assess attention, sequencing, mental flexibility and motor function. A more detailed description of each assessment measure is given in Appendix 3.2.

Two patients failed to complete a page of the SF-36 questionnaire. The missing values on these questions were calculated by taking the mean of their scores on the remaining two visits.

Statistical Analysis

The period effect was checked by paired t-tests to determine whether the patients underlying condition and ability to respond remained unchanged from first to second treatment periods. The carry-over effect was checked by independent t-tests to determine whether a response to one treatment was different in period one, as compared to period two.

Independent t-tests were conducted to determine whether there were significant differences between patients and control subjects on baseline psychological assessment scores, following appropriate tests and remedies for normality that were repeated throughout as necessary.

Psychological assessment scores were collated based on the type of treatment. Paired t-tests were then applied to the patients' and control subjects' scores separately, to determine whether to accept or reject the null hypothesis that patients' psychological assessment

scores would be no better when treated with thyroxine.

All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows[17].

RESULTS

Prior to testing the main experimental hypothesis, baseline characteristics were tested for differences. There were no significant differences in the frequency of group membership for patients and controls (χ^2 = .220, df = 1, P = .639). There was no significant difference between mean ages of patients and control subjects (t = -.145, df = 39, P = .885). Finally, there were no significant differences for frequency of previous psychiatric contact between the two groups (Fisher's Exact Sig. (2-sided) = .099). In addition, paired samples t-tests between all dependent variables at visit two and three indicated the absence of a period effect. Independent samples t-test on all dependent variables indicated that there was no carry-over effect.

TABLE 2. Scores on psychological assessment measures at baseline for patients and controls

	PATIENTS Mean ± SD	CONTROLS Mean ± SD	t	df	P value
Logical Memory I	18.68 ± 5.88	29.11 ± 6.03	-5.60	39	.000*
Verbal Paired Associates I	15.86 ± 3.54	19.00 ± 3.00	-3.04	39	ns
Visual Reproduction I	30.00 ± 6.58	33.89 ± 3.81	-2.27	39	ns
Digits Forward	8.55 ± 1.57	9.00 ± 2.31	-.746	39	ns
Digits Backward	6.95 ± 2.30	8.11 ± 2.79	-1.45	39	ns
Logical Memory II	15.09 ± 6.58	25.63 ± 7.60	-.4.80	39	.000*
Verbal Paired Associates II	6.45 ± 1.34	6.95 ± 1.18	-1.24	39	ns
Visual Reproduction II	25.32 ± 7.07	31.74 ± 5.82	-3.14	39	ns
Trail Making Test	97.50 ± 39.97	61.68 ± 16.99	3.82^	29.21	.001*
HADS	20.91 ± 8.74	8.37 ± 5.04	5.72^	34.33	.000*
Fatigue Scale	30.50 ± 8.79	15.79 ± 3.39	7.25^	27.90	.000*
SF-36 Health Survey:					
Physical Functioning (PF)	35.91 ± 30.69	87.50 ± 18.62	-6.60^	35.24	.000*
Role Physical (RP)	13.64 ± 30.06	84.21 ± 26.63	-7.82	39	.000*
Bodily Pain (BP)	37.32 ± 26.92	85.90 ± 17.88	-6.70	39	.000*
General Health (GH)	37.50 ± 24.10	84.79 ± 14.08	-7.51	39	.000*
Vitality (V)	26.60 ± 22.06	64.47 ± 17.79	-5.99	39	.000*
Social Functioning (SF)	36.93 ± 32.61	91.45 ± 16.69	-6.90	32.22	.000*
Role Emotional (RE)	33.33 ± 44.84	82.45 ± 35.78	-3.83	39	.000*
Mental Health (MH)	60.00 ± 21.42	75.37 ± 16.56	-2.54	39	ns

+ P values were calculated by Independent t-tests

^ Equality of variance not assumed by Levene's Test for Equality of Variances

Bonferroni Inequality Adjustment applied (P< .0026 for .05 level) * significant at .05 level

At baseline, patients' scores on 12 out of 19 psychological measures were significantly impaired in comparison to control subject scores ($P<.05$) (see Table 2.).

TABLE 3. Comparison of Scores for Patients on Placebo and Thyroxine

	PATIENTS				
	PLACEBO Mean ± SD	**THROXINE** Mean ± SD	t	df	P value
Logical Memory I	25.41 ± 6.94	24.82 ± 6.60	-.768	21	ns
Verbal Paired Associates I	19.23 ± 4.06	19.82 ± 2.80	.804	21	ns
Visual Reproduction I	32.05 ± 5.69	29.91 ± 6.73	-5.260	21	.000 trans *
Digits Forward	9.00 ± 1.85	9.54 ± 1.40	1.779	21	ns
Digits Backward	7.68 ± 1.99	7.86 ± 2.17	.392	21	ns
Logical Memory II	21.00 ± 1.49	21.82 ± 7.90	.643	21	ns
Verbal Paired Associates II	6.86 ± 1.32	6.83 ± 1.44	-.176	21	ns
Visual Reproduction II	26.86 ± 7.58	27.36 ± 7.51	.473	21	ns
Trail Making Test	79.95 ± 30.52	81.32 ± 31.06	.290	21	ns
HADS	14.64 ± 8.36	14.77 ± 10.01	.062	21	ns
Fatigue Scale	12.86 ± 9.40	15.32 ± 10.55	.648	21	ns
SF-36					
Physical Functioning (PF)	54.91 ± 34.20	46.14 ± 32.10	.036	21	ns
Role Physical (RP)	43.18 ± 40.22	36.36 ± 41.35	-.597	21	ns
Bodily Pain (BP)	44.55 ± 28.53	47.77 ± 27.84	.532	21	ns
General Health (GH)	48.00 ± 24.24	42.02 ± 24.24	-1.257	21	ns
Vitality (V)	41.82 ± 28.14	36.14 ± 26.94	-.662	21	ns
Social Functioning (SF)	55.68 ± 34.01	56.25 ± 31.52	.006	21	ns
Role Emotional (RE)	63.62 ± 43.53	48.47 ± 46.83	-1.11	21	ns
Mental Health (MH)	65.09 ± 21.92	61.64 ± 26.44	-.571	21	ns

+ P values were calculated by paired t-tests
trans t-test using transformed variables
Bonferonni Inequality Adjustment applied ($P < .002$ for $\alpha = .01$ level)
*significant at .05 level

TABLE 4. Comparison of scores for Controls Subjects on Placebo and Thyroxine

	CONTROLS				
	PLACEBO Mean ±SD	**THYROXINE** Mean ± SD	t	df	P value
Logical Memory I	33.10 ± 5.90	34.00 ± 4.69	.773	18	ns
Verbal Paired Associates I	21.00 ± 2.73	28.32 ± 2.80	-1.753	18	ns
Visual Reproduction I	35.63 ± 2.50	34.68 ± 3.51	-1.710	18	ns
Digits Forward	9.80 ± 2.25	9.63 ± 1.86	-.459	18	ns
Digits Backward	8.74 ± 2.08	8.26 ± 2.70	-1.184	18	ns
Logical Memory II	30.63 ± 6.36	31.42 ± 7.00	.689	18	ns
Verbal Paired Associates II	7.42 ± 1.02	7.26 ± 1.05	1.244	18	ns
Visual Reproduction II	34.42 ± 3.60	34.50 ± 3.70	.068	18	ns
Trail Making Test	54.20 ± 12.42	57.05 ± 19.16	1.058	18	ns
HADS	6.32 ± 4.60	8.63 ± 6.52	1.878	18	ns
Fatigue Scale	12.00 ± 3.80	15.32 ± 3.30	-29.543	18	.000[trans] *
SF-36 Health Survey:					
Physical Functioning (PF)	92.63 ± 9.63	91.00 ± 14.20	.681	18	ns
Role Physical (RP)	89.47 ± 19.21	79.00 ± 26.70	-1.407	18	ns
Bodily Pain (BP)	82.53 ± 24.30	80.00 ± 18.35	-.937	18	ns
General Health (GH)	84.05 ± 10.40	79.74 ± 12.21	-1.518	18	ns
Vitality (V)	73.42 ± 15.64	60.00 ± 16.83	-3.258	18	ns
Social Functioning (SF)	94.10 ± 14.05	86.16 ± 18.11	3.793	18	.001[trans] *
Role Emotional (RE)	91.70 ± 19.50	82.44 ± 28.05	4.180	18	.001[trans] *
Mental Health (MH)	79.20 ± 12.41	78.10 ± 15.00	-0.388	18	ns

[+] P values were calculated by paired t-tests

[trans] paired t-test using transformed variables

Bonferroni Inequality Adjustment applied ($p < .002$ for $\alpha = .05$ level)

*significant at .05 level

In comparing the effects of treatment, paired t-tests for patients' scores on thyroxine and placebo indicated that only one psychological measure was significantly different. Patients' mean scores on Visual Reproduction (Immediate Recall) were significantly greater on placebo ($P<.001$) (see Table 3). In a comparison of control subjects' scores on thyroxine versus placebo, three psychological measures (Fatigue Scale[14], SF-36 Social Functioning and Role Emotional[13]) were significantly different, with impaired functioning on thyroxine (see Table 4).

DISCUSSION

In terms of the treatment effect, psychological assessment scores of subjects on thyroxine in comparison to placebo indicate that thyroxine does not benefit patients or control subjects. Patients had a significantly impaired visual reproduction (immediate recall) score when treated with thyroxine. Control subjects had significantly impaired scores with regards to fatigue, social and emotional functioning when taking thyroxine. It is possible that because subjects (with the exception of one person) had normal levels of free T4 in the first instance, for some, thyroxine treatment raised their free T4 level to the extent that they began to

experience symptoms consistent with the high level of free T4 found in hyperthyroidism. These symptoms include nervousness, irritability, emotional lability and fatigue that could conceivably have had an impact on these scores. Therefore, the null hypothesis that patients' psychological assessment scores would be no better when treated with thyroxine is accepted.

There are no known experimental studies involving symptomatically hypothyroid but biochemically euthyroid patients. A comparison can, therefore, only be made to findings from studies of patients with hypothyroidism and subclinical hypothyroidism and to the recent correspondence in the BMJ detailing clinicians' observations of individual patients' responses to thyroxine in the clinic setting. The cognitive functioning, physical and mental health of the patients in this study did not benefit from thyroxine treatment. Thyroxine actually made some subjects function more poorly in certain areas. This is inconsistent with previous research that has demonstrated improvements following thyroxine treatment in patients with hypothyroidism and subclinical hypothyroidism..[6,9,18,19] In addition, these findings question whether the two symptomatically hypothyroid but biochemically euthyroid patients, observed by McLaren, Kelly and Pollock[4], who reported a marked improvement in

their condition, felt better due to thyroxine treatment.

Analysis of the psychological assessment measures at baseline show that patients were significantly more impaired than control subjects on the majority of measures. Again, a comparison can only be made to findings from studies of patients with hypothyroidism and subclinical hypothyroidism. This finding is consistent with previous research that found that patients experiencing hypothyroidism and subclinical hypothyroidism frequently experienced depressive symptoms, physical complaints, fatigue, psychomotor speed and impairment of recent memory.[6,7,9] The patients in this study did not have attention and concentration difficulties. However, Mennemier, Garner and Heilman[20] suggest that concentration may be one of the cognitive functions least affected by hypothyroidism.

The strengths of this study include the randomised design, careful attention to double blinding and a comprehensive set of valid and reliable psychological assessment measures. A control group was included who were well matched on a range of potentially confounding variables such as sex and age. There was no significant difference between patients and control groups with regards to previous psychiatric contact. Also, this study

had an adequate washout period. In some previous studies of hypothyroidism and subclinical hypothyroidism, psychological assessment measures have not been standardised, a narrow range of cognitive functions have been assessed or a control group, placebo or adequate washout period have not been included (see Chapter 2, Major Research Project Literature Review, for a full discussion).

Nonetheless, this is a preliminary study that has some limitations. These patients may have some other disorder that was not adequately assessed and could have necessitated exclusion from the study. It is possible that some of the patients may have suffered from Chronic Fatigue Syndrome, as the symptomatology of this syndrome and hypothyroidism overlap.

A small number of patients reported that they felt better on thyroxine and in certain cases this was reflected in an improvement in their psychological assessment scores. It is possible that some symptomatically hypothyroid but biochemically euthyroid patients will respond to thyroxine, but, the heterogeneous nature of the patient group in this study, in conjunction with the relatively small sample size, meant that this was not reflected in the analysis of psychological assessment scores.

A further consideration is the possibility that thyroxine was not the most appropriate drug with which to treat these patients. A recent study concluded that in patients with hypothyroidism, partial substitution with triiodothyronine (T3, the active thyroid hormone) for thyroxine might improve mood and neuropsychological function.[21] It may be that the present study should be replicated with a larger sample size and this combination of treatment.

In conclusion, this first known randomised, double blind, placebo-controlled trial demonstrates that symptomatically hypothyroid but biochemically euthyroid patients share some, but not all, of the impairments in psychological wellbeing and cognitive function of hypothyroid and subclinical hypothyroid patients. However, this is possibly where the similarity ends. Symptomatically hypothyroid but biochemically euthyroid patients do not appear to benefit from treatment with thyroxine on a wide range of psychological and cognitive measures. It is suggested that there is no empirical evidence to justify the routine prescription of thyroxine to this group of patients.

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THREE SINGLE CASE RESEARCH STUDIES (ABSTRACTS)

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Psychological intervention with parents of a child experiencing cyclical vomiting syndrome: A single case study

ABSTRACT

In the absence of a consensus regarding the aetiology and psychological management of severe cyclical vomiting syndrome (CVS) in childhood, application of the 'illness network model' (Lask and Fosson, 1989), normally concerned with more common childhood psychogenic disorders, was applied to this case. Intervention guided by this model aimed to reduce cyclical vomiting associated hospital admissions, by training parents in the application of behavioural modification techniques to the child's disturbed behaviour. However, it is postulated that intervention to reduce parental psychological distress and maladaptive family communication, commonly associated with having a CVS child, is a necessary adjunct to reducing cyclical vomiting behaviours than behaviour modification alone. Although hospital admissions were reduced, the continuing severity of childhood disturbance and parental distress highlights limited prognosis with this severely debilitating and rare disorder.

KEYWORDS

Cyclical vomiting syndrome, Child, Family, Psychological Management, Parenting Distress

Cognitive-behaviour therapy and adolescent depression: A single case study

ABSTRACT

The quality of family relationships have a significant bearing on the development and maintenance of adolescent depression (Sochet and Dadds, 1997). In the absence of empirical evidence regarding the efficacy of family involvement in cognitive-behaviour therapy (CBT) approaches to adolescent depression, this case indicates that it is possible to resolve clinically significant depression by applying the principles of CBT, against a background of chronic family dysfunction.

KEY WORDS: adolescent depression, treatment, cognitive-behaviour therapy, family conflict.

Adolescent traumatic head injury and school reintegration: A single case study

ABSTRACT

Severe traumatic head injury causes extreme changes in the life of the injured person; affecting a large number of activities and functions in different life domains (Florian, Katz and Lahav, 1991). In terms of school reintegration following injury, the primary goal is to ensure academic and social success for the young person (Ylvisaker et al., 1991). The following case presentation indicates how neuropsychological assessment can practically inform school reintegration and future educational provision for a head injured adolescent.

KEY WORDS head injury, adolescence, school reintegration.

APPENDICES